REMARKS

Claims 7-16 are now pending in the application. Claims 1-6 are presently cancelled and replaced with Claims 7-16. Claims 7-16 are fully supported in the specification and claims as originally filed. Therefore, no new matter has been introduced by way of the present amendment. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112

Claims 1-6 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. This rejection is respectfully traversed.

The Applicants will treat the above rejection as a combined 35 U.S.C. § 112, first paragraph written description rejection and an enablement rejection.

The new Claim 1 recites: "An assay to screen anti-malarial drugs by testing for binding of a test compound with plasmodium 90 kDa heat shock protein which comprises: immobilizing said test compound covalently on a matrix; reacting saponin-free Plasmodial trophozoite lysate with said covalently immobilized test compound; detecting a plasmodium 90 kDa heat shock protein bound test compound; measuring growth of *Plasmodium falciparum* in the presence of said protein bound test compound; and comparing the growth of *P. falciparum* in the presence of said protein bound test compound to the growth of *P. falciparum* in the absence of said protein bound test

compound, wherein a decrease in said measured growth of *P. falciparum* exposed to said protein bound test compound as compared to the growth of *P. falciparum* not exposed to said protein bound test compound is indicative of said protein bound test compound being an anti-malarial drug."

The Applicant has cancelled Claim 1 and has provided a new Claim 7 which is based on Claim 1. The new Claim 7 adds further limitations requiring the assay method to detect a plasmodium 90 kDa heat shock protein bound test compound; measure the growth of *Plasmodium falciparum* in the presence of the protein bound test compound; and compare the growth of *P. falciparum* in the presence of the protein bound test compound to the growth of *P. falciparum* in the absence of the protein bound test compound. If a test compound shows that it can inhibit the growth of *P. falciparum* using the amended claim steps, the test compound is said to be an anti-malarial compound. The Applicant provides ample support for the method steps and exemplifies the principle behind the screening assay using ansamycin antibiotics, geldanamycin (GA) and herbimycin A (HA). The exemplified embodiments amply demonstrate that the inhibition of PfHsp90 derived from *P. falciparum* results in the direct inhibition of growth of the malarial parasite. In other words, one of ordinary skill in the art would have concluded that the Applicant has provided ample description of the invention, i.e. the assay methodology steps to perform the inventive assay and describe the claimed subject matter in a way to confer possession of the claimed invention. The amended claims are drawn to the identification of test compounds that are capable of binding to PfHsp90, and further identification of those binding test compounds that are capable of inhibiting the growth of *P. falciparum* at the trophozoite stage. The Applicant's

description of PfHsp90 shows many physical and chemical characteristics that are representative of the genus of Hsp90 proteins.

Contrary to the allegations made in the Action, Applicant respectfully submits that the exemplified screening assays are designed to identify anti-malarial drugs and not a therapy or method for curing malaria *in-vivo*. As such, the new claims are supported by several examples (See Examples 2.0-2.2 and 3.0-3.5). These examples plainly illustrate a clear link between the inhibition of PfHsp90 at the trophozoite stage and inhibition of the organism. When GA was added at the trophozoite stage, 100% growth inhibition was observed at GA concentrations of 10μM. Thus, the Applicant has shown that the binding of a test compound to specific disease mediating target protein is indeed associated with a biological effect. There is no reason articulated why an anti-malarial test compound that is effective in inhibiting the growth of the malarial parasite *in-vitro* should not also have efficacy as a treatment *in-vivo*. The Applicants have amply demonstrated that the binding of PfHsp90 with agents other than ATP can cause an inhibition of growth of the parasite, for example when using GA. Moreover, the present amended claims require that the growth of the parasite be measured in the absence and presence of the protein bound test compound. Any speculation as to how the complexed PfHsp90-test compound would effect any pathway is not critical, since the biological effect associated with the binding between PfHsp90 and test compound is identified prior to designating the test compound an anti-malarial drug.

Applicants would like to address the Action's allegation of lack of enablement generally stated on pages 3-4 of the Office Action. Specifically, the Action states: "It would therefore seem unpredictable which compounds, if any, identified with the

disclosed methodology will be eventually shown to have therapeutic function...Applicant provides no guidance which would allow one to predict the function of any identified agent intracellularly or in vivo." (Action at page 3, lines 8-10 and 17-18). Applicant respectfully submits that the function or mode of action of the identified test compound or the dosages of the test compounds required for *in-vivo* activity are wholly irrelevant to the exemplified screening assays. An anti-malarial drug is a drug that inhibits the growth of the malarial parasite. The Applicant is not claiming a method for treating malaria with an anti-malarial drug. If the claims were drawn to a method for treating a subject with malaria, then the function, dose, route of administration and other indicia of treatment steps may bear relevance to the enablement of such claims. However, it is respectfully submitted that the amended claims recite a growth inhibition step which is perfectly capable of identifying anti-malarial drugs, which can later be tested for activity, toxicity, pharmacokinetics, dosages, route of administration and the like. Such considerations, however, have no bearing on the present claims.

The Applicant has amply and adequately described how to make and use the present screening assays, including, design of the assay as shown in Examples 3.0-3.4 (shown on pages 8-10 of the specification) and inhibition of the parasite as shown in Example 3.5 (shown on page 11). The Applicant therefore, respectfully submits, that the new Claims 7 and 15 are adequately described, and are fully enabled by the specification as originally filed. Claims 8-14 and 16 are patentable by virtue of their dependency on the independent Claims 7 and 15.

Accordingly, the Applicant requests that the Examiner reconsider and withdraw the present rejection of Claims 1-6 and find that the new Claims 7-16 are patentable for at least the reasons provided above.

Claims 1-6 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

The Applicant has cancelled Claims 1-6 and has replaced these claims with the new Claims 7-16. Support for the new claims can be found in the specification as originally filed and in the cancelled Claims 1-6. The terms "known" "such as" "suitable matrices" and "novel" have been deleted. Furthermore, the new Claims 7-16 have deleted reference to the term "use" or "using". The new Claims 7-16 provided herewith, have been prepared in conformance with standard US patent drafting practices and positively recite active, positive method steps such as immobilizing, reacting, detecting, measuring and comparing as shown in Claim 7.

The Applicant has also concluded with a method step in the independent claims including the preamble of the claim as suggested by the Examiner. The Applicant has also corrected the lack of antecedent basis for the terms binding, test compound, compound bound Plasmodial 90kDa heat shock protein, amine coupling kit, unreacted moieties, change in refractive index and BIAcore SA chip. The acronyms DMSO and TNESV have been defined in the claims at their first appearance as suggested.

In addition, the Applicant has removed reference to trade names/trademarks to overcome the present rejection of the use of these trade names and trademarks in the claims, thereby rendering this portion of the rejection moot.

It is respectfully submitted that all of the perceived indefiniteness issues alleged in the present Action on pages 5-6, have been accommodated or rendered moot by the cancellation of Claims 1-6. The new Claims 7-16 do not recite the alleged deficiencies under 35 U.S.C. § 112, second paragraph enumerated in the Action on pages 5-6 with respect to Claims 1-6.

Accordingly, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of Claims 1-6 and find that the new Claims 7-16 are not indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-4 and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jendoubi et al. (J. Immunol. 134: 1941, 1985, hereinafter referred to as "Jendoubi") in view of Bonnefoy et al. (Mol. Biochem. Parasitol. 67: 157, 1994, hereinafter referred to as "Bonnefoy") and Banumathy et al. (J. Biol. Chem. 277: 3902, 2002, hereinafter referred to as "Banumathy"). This rejection is respectfully traversed.

Jendoubi is drawn to the isolation of a monoclonal antibody that bound to a polypeptide from *Plasmodium falciparum* having an apparent molecular weight of 90,000 Da. Identification of the 90,000 Da. polypeptide to be PfHsp90 is alleged to be supplied from Bonnefoy. Bonnefoy is drawn to the characterization of the *P. falciparum* Pfhsp90 polypeptide by nucleotide sequencing. The Action recites that the use of saponin in the extraction of PfHsp90 from host hsp 90 was provided by the teachings of

Banumathy. In addition, other references made of record and not relied upon which were considered pertinent by the Examiner are allege to teach HSp90 binding assays.

The Applicant respectfully submits, that the cited art of record fail to teach each and every claim limitation of the newly added independent Claims 7 and 15 and therefore, fails to raise a *prima facie* case of obviousness with respect to these newly added claims. (See MPEP § 2143.03). The new Claim 7 recites measuring growth of *Plasmodium falciparum* in the presence of said protein bound test compound; and comparing the growth of *P. falciparum* in the presence of said protein bound test compound to the growth of *P. falciparum* in the absence of said protein bound test compound, wherein a decrease in said measured growth of *P. falciparum* exposed to said protein bound test compound as compared to the growth of *P. falciparum* not exposed to said protein bound test compound is indicative of said protein bound test compound being an anti-malarial drug.

One of ordinary skill in the art would not have concluded that a screening assay for the identification of anti-malarial drugs could be established from the teachings of Jendoubi, in view of Bonnefoy and Banumathy. None of the references describe the use of immobilized test compound and steps for identifying which test compound(s) is/are capable of binding to PfHsp90 followed by growth and inhibition steps as recited in the various exemplified embodiments. It has been the inventor's work that has identified that some compounds immobilized on a matrix which specifically bind to PfHsp90 can also inhibit the growth of the parasite during the early trophozoite stage and function as an anti-malarial agent. Jendoubi teaches that a monoclonal antibody is capable of binding to its cognate antigen Pfhsp90, which is qualitatively different from

test compounds that bind using an activity associated motif located in the PfHsp90 protein such as, an ATP binding site, or a geldanamycin binding site. Jendoubi teaches away from using PfHsp90 as a target site because Jendoubi teaches that the monoclonal antibody XIV-7 which specifically binds to PfHsp90 had no inhibitory effect on the parasite. One of ordinary skill in the art, would not have arrived at the Applicant's invention on the basis of Jendoubi in view of Bonnefoy and Banumathy because there was no motivation or suggestion to use PfHsp90 as a target site for inhibition of the malarial parasite and as such, the use of PfHsp90 as a binding target for screening anti-malarial test compounds is not rendered obvious on the basis of any single or combination of references cited of record.

For at least these reasons, the present Action fails to make a *prima facie* case of obviousness of new Claims 7 and 15 and dependent claims thereon, over the cited combination of references. Notwithstanding the Action's remarks with respect to Claims 1-4 and 6, Claims 8-14 and 16 each embody all of the claim limitations of Claim 7 and 15 respectively from which they depend or which they reference, and are therefore nonobvious at least for the same reasons that Claims 7 and 15 are nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is similarly nonobvious. MPEP §2143.03. Moreover, several dependent claims are also non-obvious in their own right. For example, Claims 9, 10-14 and 16 each recite claim limitations that are neither taught nor suggested in any of the references cited of record.

Accordingly, the Applicant respectfully requests the Examiner to reconsider and withdraw the present rejection of Claims 1-4 and 6 and find that the new Claims added

herein are similarly not obvious under 35 U.S.C. § 103(a).

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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